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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,315	01/16/2004	Gregory T. Bleck	GALA-08484	9065
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MEDLEN & CARROLL, LLP 101 HOWARD STREET SUITE 350 SAN FRANCISCO, CA 94105			EXAMINER POPA, ILEANA	
			ART UNIT 1633	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/759,315	Applicant(s) BLECK ET AL.	
	Examiner Ileana Popa	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 12, 14-18, 20-28 and 30-41 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-10, 12, 14-18, 20-28 and 30-41 is/are rejected.
- 7) ☒ Claim(s) 27 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01/16/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 11, 13, 19, 29, and 42 have been cancelled. Claims 1 and 21 have been amended.

Claims 1-10, 12, 14-18, 20-28, and 30-41 are pending and under examination.

Response to Arguments

Specification

3. The objection to the specification for containing trademarks is withdrawn in response to Applicant's amendments to the specification filed on 01/30/2007.

Drawings

4. The objection to the drawings for containing sequence listings is withdrawn in response to Applicant's arguments filed on 01/30/2007.

Claim Objections

5. Claim 27 remains objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim for the

reasons of record set forth in the non-final Office action of 10/26/2006. Applicant did not provide any argument regarding the instant objection.

** It is noted that claims 28 and 30-34 are dependent on claim 27.

Double Patenting

6. Claims 1-10, 18, 20-28, 30-34, 39, and 41 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-20, 22, 28-37, 42-46 of copending Application No. 10/397079 because Applicant did not submit a terminal disclaimer.

7. Claims 1-10, 12, 14-18, 20-28, 30-34, and 39-41 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 9-12 and 14-22 of U.S. Patent No. 6,852,510 because Applicant did not submit a terminal disclaimer.

8. Claims 1-10, 12, 14-18, 20-28, 30-34, and 39-41 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 110-124 of copending Application No. 11/018,895 because Applicant did not submit a terminal disclaimer.

Claim Rejections - 35 USC § 112, 2nd paragraph

9. The rejection of claims 1-10, 14-18, 20-28, and 30-41 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's arguments filed on 01/30/2007.

10. The rejection of claim 21 is under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's arguments filed on 01/30/2007.

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

11. Claims 1-10, 12, 14-18, 20-28, and 30-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the non-final Office action of 10/26/2006. Applicant's arguments filed 01/30/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the specification clearly contemplates any number of integrations within the range specified, i.e. the specification discloses that "in some embodiments, the genome comprises at least 5, and preferably, at least 100 integrating integrated vectors" (p. 3, lines 25 and 26). Therefore, Applicant submits that the range of 20 to 100 integrated vectors is clearly within the described range of 5 to 100 integrated vectors per cell. Applicant also points out to *In re Wertheim* as supporting the argument that the claimed range does not represent new matter and requests the withdrawal of the rejection.

Applicant's arguments have been considered, however, the rejection is maintained for the following reasons:

It is noted that the case of *In re Wertheim* the specification disclosed a range of 25-60% and provided a specific example of 36% that supported the new lower limit of 35% (which is very close to 36%), and therefore the new range of 35-60% was not considered new matter. In the instant case, however, the specification does not provide any specific example disclosing 20 integrants or a value close to 20. The specification broadly discloses a range from 2 to 100 integrations, preferably from 5 to 50 (p. 17, paragraph 0182), with no example showing 20 integrations. Even if the range of 20-100 is within the range of 2-100 taught in the specification, there is no support in the specification to specifically select the lower limit of 20. The specification provides support only for the lower limits of 2 and 5. For these reasons, the rejection is maintained.

Claim Rejections - 35 USC § 103

12. Claims 1-10, 12, 14, 18, 20, 21, 27, 28, 30-34, and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. (1996, cited in form PTO-892 on 05/18/2005), in view of both Felts et al. (1999, cited in form PTO-892 on 05/18/2005) and Inaba et al. (1998, cited in form PTO-1449 on 05/18/2005) for the reasons of record set forth in the non-final Office action of 10/26/2006. Applicant's arguments filed 01/30/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Mathor et al. do not teach or suggest the limitation of 20 to 100 integrations and the other cited references do not cure this defect. Applicant argues that even if it would be obvious to use different MOI to achieve the claimed ranges, there is no suggestion in the references to make cells with these ranges. Applicant submits that, when the full field of the invention is considered, a person of skill in the art would not combine or modify the cited references to provide the claimed integration ranges. Applicant points out that references such as Coffin (Applicant's IDS) and Arai et al. (Virology, 1999, 260: 109-115) teaching away from the claimed invention. Applicant submits that (i) Coffin teaches that, since proviral insertion can cause the inactivation of tumor suppressor genes and the activation of oncogenes, insertional mutagenesis by retroviral vectors is a safety concern (p. 463, column 1), and (ii) Arai et al. teach that proviral integration with a very high copy number seems to cause cell death. Applicant argues that one of skill in the art knowing these references would not be motivated to use different MOIs to achieve the claimed number of integrations (and therefore, to increase gene expression) because the art teaches that high levels of integration are undesirable and that none of the cited references teach or suggest the desirability of the claimed range of integrations. Applicant further submits that the Examiner used hindsight and requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the claims remain rejected for the following reasons:

The argument that the Examiner failed to establish a *prima facie* case of obviousness because Mathor et al. taken with Felts et al. do not teach or suggest the

Art Unit: 1633

limitation of 20 to 100 integrations is not found persuasive because the motivation to combine the prior art does not have to be stated by the prior art; the rationale to combine may be implied from the prior art or may be reasoned from the knowledge available to one of skill in the art at the time the invention was made (see MPEP, 2144, Sources of Rationale Supporting a Rejection Under 35 U.S.C. 103). Mathor et al. clearly teach that the synthesis of the exogenous protein encoded by the viral vector is proportional to the number of proviral integrations (Abstract, p. 10371, column 2, p. 10373, Table 1). Felts et al. clearly teach controlling the copy number of integrated provirus by varying the multiplicity of infection (MOI) (p. 16). Based on these teachings, one of skill in the art would have known to increase the production of a desired protein by increasing the number of viral integration and would have known to increase the number of viral integration by increasing the MOI. One of skill in the art would have been motivated to do so in order to achieve a higher production of the desired protein. Regarding the argument that Coffin teaches that insertional mutagenesis by retroviral vectors is a safety concern, it is noted that Coffin refers to the *in vivo* use of retroviral vectors in animals and humans. Safety concern is not an issue in the instant case, because the claims encompass a host cell *in vitro* and the combined teachings of Mathor et al. and Felts et al. are drawn to the *in vitro* production of recombinant proteins. Regarding Arai et al., they teach that the number of proviral integrations (and therefore, protein production) can be increase by increasing MOI (p. 112, column 1, Fig. 3) and that 15 integrations can be obtained with a MOI of 30. Although they teach that proviral integration with a very high copy number seems to cause cell death, Arai et al.

do not teach what a very high copy number means, i.e., they do not correlate a MOI of 100 to any specific integration number (it is noted that the art teaches 1000 integration events or more as a very high copy number, whereas 30-300 integration events are considered moderate copy numbers, and wherein these integration events do not result in cell death; see Taruscio et al., *Chromosoma*, 1991, 101: 141-156, p. 141, column 2).

Arai et al. teach that only very high levels, and not moderate copy levels, cause cell death. Therefore, the teachings of Arai et al. do not exclude using MOIs lower than 100. Based on these teachings, one of skill in the art would have known to use MOIs between 30 and 100 to obtain more than 15 integrations and would have known to use the routine experimentation taught by the art to determine what MOIs result in 20 to 100 integrations. Even assuming that a MOI of 100 would be used, Arai et al. do teach that not cells are dying and therefore, one of skill in the art would have known to use routine experimentation to clone the viable cells that contain a very high number of integration events and produce cell lines that synthesize high amounts of recombinant protein.

Therefore, the art does not teach away from the claim invention. In response to Applicant's argument that one of skill in the art would not be motivated to attained the claimed ranges, it is noted that the art teaches the number of integrations per cell as being a result-affecting variable and therefore, one of skill in the art would be motivated to use a range of integrations (obtained by varying MOIs) to obtain optimum results. One of skill in the art would use only routine experimentation to optimize the results, and by doing this one of skill in the art would have necessarily obtained integrations within the broad range of 20 to 100. In response to Applicant's argument that the examiner's

Art Unit: 1633

conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

13. Claims 1-10, 12, 14-18, 20, 21, 26, 27, 28, 30-34, and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., as applied to claims 1-10, 12, 14, 18, 20, 21, 27, 28, 30-34, and 41 above, in further view of Burns et al. (1993, cited in form PTO-1449 on 05/18/2005) for the reasons of record set forth in the non-final Office action of 10/26/2006. Applicant's arguments filed 01/30/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Burns et al. do not cure the deficiencies noted in the combination of Mathor et al., Felts et al., and Inaba et al., because Burns et al. do not teach or suggest the claimed range of 20 to 100 integrants. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the claims remain rejected for the reasons stated above. It is noted that Burns et al. was cited for teachings other

Art Unit: 1633

claim limitations (i.e., pseudotyped retrovirus) and not for teaching claimed range of 20 to 100 integrants. Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

14. Claims 1-10, 12, 14, 18, 20, 21, 26, 27, 28, 30-38, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., as applied to claims 1-10, 12, 14, 18, 20, 21, 27, 28, 30-34, and 41 above, in further view of Schroder et al. (1997, cited in form PTO-892 on 05/18/2005) for the reasons of record set forth in the non-final Office action of 10/26/2006. Applicant's arguments filed 01/30/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Schroder et al. do not cure the deficiencies noted in the combination of Mathor et al., Felts et al., and Inaba et al., because Schroder et al. do not teach or suggest the claimed range of 20 to 100 integrants. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the claims remain rejected for the reasons stated above. It is noted that Schroder et al. was cited for teachings other claim limitations (i.e., amplifiable marker) and not for teaching claimed range of 20 to 100 integrants. Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

15. Claims 1-10, 12, 14, 18, 20-24, 26, 27, 28, 30-34, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and

Art Unit: 1633

Inaba et al., as applied to claims 1-10, 12, 14, 18, 20, 21, 27, 28, 30-34, and 41 above, in further view of both Primus et al. (1997, cited in form PTO-892 on 05/18/2005) and Kolb et al. (Hybridoma, 1997, 16: 421-426, Abstract) for the reasons of record set forth in the non-final Office action of 10/26/2006. Applicant's arguments filed 01/30/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that the combination of Primus et al. and Kolb et al. do not cure the deficiencies noted in the combination of Mathor et al., Felts et al., and Inaba et al., because neither Primus et al. nor Kolb et al. teach or suggest the claimed range of 20 to 100 integrants. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the claims remain rejected for the reasons stated above. It is noted that Primus et al. and Kolb et al. were cited for teachings other claim limitations (i.e., expressing monoclonal antibodies into a cancer cell and bicistronic expression cassette, respectively) and not for teaching claimed range of 20 to 100 integrants. Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

16. Claims 1-10, 12, 14, 18, 20, 21, 25, 27, 28, 30-34, and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with Felts et al. and Inaba et al., as applied to claims 1-10, 12, 14, 18, 20, 21, 27, 28, 30-34, and 41 above, in further view of Naldini et al. (1996, cited in form PTO-892 on 05/18/2005) for the

Art Unit: 1633

reasons of record set forth in the non-final Office action of 10/26/2006. Applicant's arguments filed 01/30/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that Naldini et al. do not cure the deficiencies noted in the combination of Mathor et al., Felts et al., and Inaba et al., because Naldini et al. do not teach or suggest the claimed range of 20 to 100 integrants. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the claims remain rejected for the reasons stated above. It is noted that Naldini et al. was cited for teachings other claim limitations (i.e., lentiviral vector) and not for teaching claimed range of 20 to 100 integrants. Therefore, the claimed invention was *prima facie* obvious at the time the invention was made.

Conclusion

17. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

Art Unit: 1633


the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Weitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD


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